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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/635,196	08/06/2003	David Warburton	9022-21CT	8327

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/635,196	WARBURTON ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7,13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Final Rejection

Claims 1, 3-5, 7, and 13 are pending.

Applicant's traversal and the amendment to claims 1, 7 and 13 in paper filed on 3/1/06 is acknowledged and considered by the examiner.

Priority

The status of the parent application (ABN) is missing on the first of the instant specification.

Applicant's arguments filed 3/1/06 have been fully considered but they are not persuasive.

Applicant argues that the number of the provisional application has been corrected and the status of the parent application has been inserted.

Applicants corrected the provisional application but did not insert that status of the parent application. Thus, the status of the parent application is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5, 7, 9, 10, and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The field of the invention embraces a method of stimulating the growth of lung alveolar surface in a lung of a mammal comprising: providing alveolar epithelial type 2 (AEC2) cells to said lung (complete or a fraction of a lung) in an amount sufficient to regenerate the lung alveolar surface in the lung.

The state of the art for tissue restoration displays that cell transplants have been used in several areas, (Stocum et al., Wound Rep Reg, Vol. 6, pp. 276-290, 1998). Stocum teaches that over the past 50 years, we have made progress in our ability to replace body parts with devices, solid organs, and tissue transplants, or both (page 277). Such replacement parts, however, still pose significant biological problems, and they are not useful for all situations (page 277). Furthermore, Stocum teaches that providing reliable sources of cells for cell transplant is crucial issue that requires establishing culture banks or proliferating stem, progenitor, or differentiated cells that can be drawn on as required, as well as cell culture media that support the proliferation and differentiation of these cells (page 284).

Furthermore with respect to lung transplantation, the state of the art for lung transplantation has gained widespread acceptance as a therapeutic option for a diverse array of lung diseases as taught by Arcasov et al. (Medical Progress, Vol. 340, pages 1081-1091. Nonetheless, complications are frequent and result constraints on long-term preservation of graft function and patient survival (page 1081). The common complications are primary graft failure,

airway complications, infection, acute rejection, and chronic rejection (pages 1087-1088). Lung transplantation that reaches its current clinical plateau largely through refinements in the selection of patients, operative techniques, and postoperative care (page 1088). Two major hurdles must be overcome to increase the applicability of lung transplantation and improve long-term results: the supply of donor organs must be increased to meet the demand, and chronic rejection must be more effectively prevented (page 1088).

In addition, with respect to lung stem cells, the state of the art as exemplified by Magdaleno et al., (Adv Pediatr, Vol. 45, pp. 363-96, 1998), Magdaleno teaches that before stem cells can used for therapeutic purposes understanding tissue genetics and immunology is essential (pages 363-364). Animal models or repair provide some clues about which cells are the stem cells in the lung (page 373). However, this approach is complex and oftentimes it is difficult to identify the specific molecular events that govern lung cell gene expression (page 373). In the course of studying the evidence for specific stem cells in the lung, one consensus perpetually emerges: the processes of lung development, gene regulation, and injury repair are multi-step processes involving a concerted effort between extracellular and intracellular input to elicit proliferation and/or differentiation of specific epithelial cell types of the airways (page 388). Wu further supports the unpredictability of lung stem cells and progenitor cells (Stem Cells and Development 13:607-613, 2004). "The lung employs a myriad of cell phenotypes in its unique function of inhaling and expiring air (page 607)." "Due to this structural complexity, transdifferentiation of stem cells into the lung is particularly complicated (page 607)."

The disclosure provides working examples: Example 1 (pages 10-16) displays that exogenous fibroblast growth factor 10 (fgf10) can stimulate wild type lung morphogenesis and

rescues cells that were exposed to nitrogen in an *in vitro* cultures of murine lung cells. Example 2 (pages 16-22) encompasses hyperoxia treatment of adult rat and fetal rat alveolar epithelial type 2 cells (AEC2) isolated in cell cultures. The results from example 2 show that telomerase activity is observed in rat fetal AEC2 and can be re-induced in adult AEC 2 following hyperoxic injury. Furthermore, the disclosure contemplates a method of inducing lung regeneration by autologous stem cell replacement, wherein the stem cells are genetically modified (pages 9-10). The applicant does not provide a working of the claimed method. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The specification provides sufficient guidance for one skilled in the art to use exogenous fgf10 to stimulate growth in an *in vitro* culture of murine lungs cells. However, this does not reasonably extrapolate to the claimed invention because the specification fails to provide sufficient guidance in several critical areas which encompass: 1) how to remove a lung or portion thereof, 2) how to culture AEC2 cells to prevent quick dedifferentiation (See Wu (supra), page 610, left column), 3) how to administer said cells to said lung or portion thereof, 4) what amount is sufficient to regenerate lung alveolar surface, 4) how to avoid a graft vs. host response in a mammal undergoing a lung transplant, and 5) how to transplant a lung into a mammal. The prior art does not provide the teaching that is lacking from the specification to display that is was routine procedure to practice the method. The specification fails to provide sufficient guidance for how stimulating murine lung cells *in vitro* can reasonably correlate to any method for treating a mammal that needs growth of the lung alveolar surface using AEC2 cells in a method of cell therapy. In view of the art of record, which teaches, "drawing analogies from the studies performed in rodents to human lung development raises certain caveats, however, because lung

development in humans differs from that observed in rodents, See pages L1197-L1198 (Driscoll et al., Am J Physiol Lung Cell Mol Physiol, Vol. 279, pp. 1191-98, 2000)." Furthermore, Driscoll teaches that, "the data presented in the disclosure raises question to whether telomerase expression in the repairing lung is simply a marker for proliferation and whether it is expressed more ubiquitously than would be expected for a stem cell population (page L1196)." In addition, Driscoll teaches that, "because no method exist at the time the application was filed and currently for following the fate of individual cells in the lung, it is impossible to determine when and how telomerase expression is induced an how long it persists in each individual cell (page L1197)." In view of In Re Wands Factors, it would take one skilled in the art an undue amount of experimentation to reasonably correlate from the disclosure of contemplating a cell therapy method for regenerating the lung alveolar surface in a mammalian lung for a therapeutic result. In view of the concerns stated by the art of record, the specification does not provide sufficient guidance for one skilled in the art to make and/or use AEC2 cells in a method of regenerating lung alveolar surface in a mammal's lung. Thus, the disclosure is not considered enabled for the claimed invention.

In conclusion, the specification and instant claims coupled with the art of record do not provide reasonable enablement for the claimed invention. In view of the state of the art for lung transplantation, cell therapy, wherein the method is employed to correct a genetic disorder in a genus of mammals was unpredictable at the time the invention was made, the lack of sufficient guidance to any therapeutic method of stem cell therapy, the breadth of the claims, one skilled in the art could not make and/or use the invention without undue experimentation.

Applicant's arguments filed 3/1/06 have been fully considered but they are not persuasive.

In response to applicant's argument that abstracts of various publications, which predate the filing date of this application demonstrate that the art of lung transplantation was sufficiently developed at the time the application was filed in 1999 to expect that transplantation as described in the claimed methods could be carried out using routine procedures, the argument is not found persuasive because while it is acknowledged that lung transplant has been performed in the prior art, the claimed method is directed regenerating alveolar surface area in a lung (in vivo or ex vivo) and lung transplantation. Neither the specification nor the prior art (e.g., Wu (supra), page 610, left column and Mason et al. American Journal of Respiratory Cell and Molecular Biology 16, 359-360, 1997) disclose a method for regenerating alveolar surface area in a lung using stem cells (AEC2).

In response to applicant's argument that there is no requirement that an invention address or overcome all obstacles in a field in order to be enabling, the argument is not found persuasive because "The focus of the examination inquiry is whether everything within the scope of the claim is enabled." "Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims." See, e.g., AK Steel Corp. v. Sollac, 344 F.3d 1234, 1244, 68 USPQ2d 1280, 1287 (Fed. Cir. 2003). The specification does not specify the dosage or method of use and it is not known to one skilled in the art that such information could be obtained without undue experimentation. Mason et al. (supra).

The Declaration of Barbara Driscoll, Ph.D. under 37 CFR 1.132 filed 3/1/06 is insufficient to overcome the rejection of claims 1, 3-5, 7, and 13 based upon 112 first paragraph enablement rejection as set forth in the last Office action because: the declaration does not support the contemplation of the claimed method in the specification. The specification does not disclose the working example in the declaration (engrafting AEC2 expressing a marker gene into lungs of a mouse). The skilled artisan would not have been able to reasonably extrapolate from the contemplation in the specification to the working example in the Declaration to practice the claimed method without an undue amount of experimentation. See Warburton et al., page 988, left column. Thus, there is no nexus between the claimed method and the working example in the Declaration. Other than the assertion in the Declaration that AEC2 can regenerate alveolar surface area in a lung, the Declaration does not provide sufficient guidance and/or factual evidence that delivering AEC2 cells to a mouse resulted in regeneration alveolar surface area in a lung. The Declaration displays that AEC2 cells expressing a marker gene can be injected into a mouse an engrafted into lung tissue. The Declaration does not display where in the lung the cells where engrafted and if the cells would able to regenerate alveolar surface. The skilled artisan understands that when cells are administered to an animal, some cells end up in the lung (e.g., the lung is one of the first areas that cells metastasize to or cells get lodged in the branches of a lung after cell therapy). See Grove et al. abstract, 3394. Thus, the showing of cells being engrafted in the lung does not reasonably correlate to regenerating alveolar surface area in a lung (in vivo or ex vivo).

Response to Arguments

Applicant's arguments, see pages 5-7, filed 3/1/06, with respect to 112 first paragraph written description and new matter rejection have been fully considered and are persuasive. The rejection of claims 1, 3-5, 7, and 13 has been withdrawn because of the amendment to claims 1 and 13.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, SPE – Art Unit 1635, can be reached at (571) 272-4517.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman